This memo and the attached documents request permission for a Single Patient Compassionate Treatment protocol. The patient has EBV associated lymphoma. I wish to treat · with retrovirally-marked autologous EBV-specific cytotoxic-T lymphocytes (CTLs). These cells have been prepared by the St. Jude Children's Research Hospital of Memphis, TN, and will be used as a single exemption and extension to their attached protocol with pending approval from the NIH Institutional Biosafety Committee, the Office of Recombinant DNA Activities, and the FDA, in addition, to the NIAID IRB and the NIH Clinical Center.

Attached are documents relevant to this request. It should be noted that at this time the patient and l · mother have not signed the consent form. Approval of the single patient protocol is so complicated that I will not invite the patient and initiate the treatment until I know that all of the approvals have been obtained and the cells are available for infusion.

History of Present Illness:

The patient is a female with Epstein-Barr Virus associated with lymphoproliferative disorder who initially presented in September 1993 with cervical adenopathy and bilateral pulmonary infiltrates. The patient later developed hepatosplenomegaly and cutaneous vasculitis. The patient initially responded to steroid treatment, however, recurrent paratracheal adenopathy lead to a surgical resection of lymph nodes in the neck in May 1994. In August 1994, the patient was diagnosed with sleep apnea which was treated with surgical debulking and steroids. In May 1995, a lymph node biopsy showed a polyclonal B-cell lymphoma and alpha-interferon was tried for five months without adequate response. More recent lymph node biopsy

revealed progression of the tumor histology to that of an oligoclonal B-cell lymphoma with effacement of the lymph node architecture. The patient was advised through NCI consultation to undergo multidrug methotrexate, 6-MP, chemotherapy. The family initially refused but later accepted administration of vincristine, cytoxan, and prednisone when it became apparent that the tumor had infiltrated small bowel, caused partial obstruction, and threatened perforation. On this 3 drug regimen for the past year, the patient has stabilized but continues to have a substantial tumor burden with markedly enlarged lymph nodes in several chains.

The relationship of EBV to the tumor is based on persistently high EBV-specific antibody titers with a VCA-IgG 1:10,240, and repeated positive tissue studies showing EBV latent antigens and EBV specific RNA by in situ hybridization.

This patient's prior medical history is also relevant to this compassionate request. Early in childhood it became apparent that must possess some still undefined cellular immune deficiency. experienced a severe and undiagnosed bout of encephalitis, and severe herpetic stomatitis. The encephalitis resulted in hydrocephalus necessitating placement of a V-P shunt. There are residual intellectual deficits such that possesses the intelligence of a 6-8 year old. The stomatitis caused severe scarring and retraction of the tongue so that speech is significantly impaired.

Rational for CTL Therapy:

The rationale for using EBV-specific CD8 positive CTLs is explained in detail in the attached protocol from St. Jude's. Briefly, CTLs are thought to be the most important defense mechanisms against outgrowth of EBV-infected B cells. Evidence to support its use in the treatment and control of EBV associated lymphoproliferative diseases derives from the published experience with EBV-specific CTLs in two general settings. The first involves donor lymphocytes administered to patients with EBV associated lymphomas arising after bone marrow transplantation. Early studies have shown this approach to be remarkably promising (Papadopoulos et.al., NEJM 330:1185, 1984 and Rooney, et.al., Lancet 1:344, 1995. The studies in bone marrow transplant recipients involved allogeneic donor CTLs. The group at St. Jude's has also begun administration of autologous EBV-specific CD8 positive CTLs for the treatment of EBV-positive Hodgkin disease (attached protocol).

To follow the fate of the transfused autologous CTLs, the investigators at St. Jude's transduce the cells ex-vivo with a standard retro virus vector expressing a neomycin resistance gene. They have detected persistence of infused, marked CTLs for at least twelve weeks.

' St. Jude's has already received a sample of peripheral blood and has generated EBV-specific CTLs from them.

colleagues are prepared to expand those cells, retrovirally marked ex-vivo and ship us the cells for infusion here. They are willing to obtain and analyze serial blood specimens as required per their protocol to study the distribution and fate of infused T cells.